Quantitative Imaging of Small Tumours with Positron Emission Tomography

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2020

document version
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QI-1-PET

Chapter 8

Prognostic Value of [^{18}F]-Fluoromethylcholine PET-CT before Stereotactic Body Radiation Therapy for Oligometastatic Prostate Cancer

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Int J Radiat Oncol Biol Phys. 2018 Jun 1;101(2):406-410.

Abstract

Purpose: Treating oligometastases detected by [^{18}F]-fluoromethylcholine positron-emission tomography/computed tomography (PET/CT) with stereotactic body radiotherapy (SBRT) may postpone initiation of androgen-deprivation therapy, and possibly prolong progression-free survival (PFS). However, better prognostic factors are needed to improve patient selection. We investigated the predictive value of [^{18}F]-fluoromethylcholine-PET/CT-derived parameters on PFS in oligometastatic prostate cancer patients treated with SBRT.

Methods and Materials: In [^{18}F]-fluoromethylcholine PET/CT scans of forty consecutive patients with ≤4 metachronous metastases treated with SBRT we retrospectively measured the number of metastases, standardized uptake values (SUVmean, SUVmax, SUVpeak), metabolically active tumour volume (MATV), and total lesion choline uptake (TLCU). Partial-volume correction was applied using the iterative deconvolution Lucy-Richardson algorithm.

Results: 37 lymph node and 13 bone metastases were treated with SBRT. 33 patients (82.5%) had 1 lesion, 4 (10%) had 2 lesions, and 3 (7.5%) had 3 lesions. After a median follow-up of 32.6 months (IQR 35.5), the median PFS was 11.5 (95%CI 8.4-14.6). Having more than a single lesion was a significant prognostic factor (HR=2.74; p=0.03), and there was a trend in risk of progression for large MATV (HR=1.86; p=0.10). No SUV or TLCU was significantly predictive for PFS, regardless of partial-volume correction. All PET semi-quantitative parameters were significantly correlated with each other (p≤0.013).

Conclusion: The number of choline-avid metastases was a significant prognostic factor for progression after [^{18}F]-fluormethylcholine PET/CT-guided SBRT for recurrent oligometastatic prostate cancer, and there seemed to be a trend in risk of progression for patients with large MATVs. The lesional level of [^{18}F]-fluoromethylcholine uptake was not prognostic for progression.

Introduction

For hormone-sensitive metastatic prostate cancer first-line treatment commonly consists of androgen deprivation therapy (ADT) with or without chemotherapy (*1,2*). While effective in deferring disease progression, side-effects can compromise quality of life (*3*). There is growing interest in local therapy for oligometastatic disease (e.g. stereotactic body radiotherapy, SBRT) with the aim of achieving prolonged progression-free survival (PFS) and postponing or avoiding initiation of ADT (*4-9*). However, reported PFS and ADT-free survival rates are variable and often limited (*5*). Therefore, prognostic or predictive biomarkers are urgently needed.

[^{18}F]-fluoromethylcholine PET/CT may provide prognostic information in prostate cancer patients (*10-12*). We therefore comprehensively explored the potential prognostic value of semi-quantitative [^{18}F]-fluoromethylcholine PET-derived metrics in SBRT-treated oligometastatic patients.

Materials and Methods

Patients

We included 40 consecutive patients with PSA relapse after primary local treatment for prostate adenocarcinoma, with oligometastases (≤4 lesions) detected at [^{18}F]-fluoromethylcholine PET/CT, treated with SBRT between January 2009 and December 2015, without ADT during SBRT. Clinical results have been reported [9]. Standard dose-fractionation schedules were 5x7Gy and 3x10Gy. Biochemical progression after SBRT was defined as PSA rising ≥25% or ≥2.0 ng/ml above baseline or post-SBRT nadir, documented on two consecutive measurements. Our institutional medical ethics committee waived the need for informed consent.

PET/CT

Forty (±9) minutes after injection of 336±68MBq [^{18}F]-fluoromethylcholine (4MBq/kg) patients underwent whole body [^{18}F]-fluoromethylcholine PET/CT (n=37 Gemini/Ingenuity [Philips Healthcare], n=3 Biograph [Siemens]; EARL-accredited), with image reconstruction compliant with EANM standards (*13*). We analysed lesions on volume-of-interest basis, yielding mean standardized-uptake-value (SUV, equation 1) with and without correction for partial-volume effects by

Lucy-Richardson iterative deconvolution (SUV_{mean}, SUV_{pvc}, resp.), SUV_{max}, SUV_{peak}, metabolically active tumour volume (MATV), and total lesion choline uptake ($TLCU_{pvc}$). Within patients, we calculated both highest and total MATV and TLCU in case of multiple lesions (indicated as suffix). Tabular data of uncorrected SUV_{mean}, SUV_{max}, SUV_{peak} and uncorrected TLCU are presented as supplemental data, available at https://www.redjournal.org/.

$$\text{SUV} = \frac{Activity\ Concentration\ (^{Bq}/_{mL})}{Injected\ Dose\ (Bq)/\ bodyweight\ (g)} \qquad \text{Eq.1}$$

Statistical analysis

Survival analysis was performed using the Kaplan-Meier method, univariate Cox-regression, and log-rank test (variables were dichotomized). Besides quantitative PET-parameters, we analysed several other potential prognostic factors (number of choline-avid lesions, lesion type, prior ADT treatment, Gleason score, PSA at metastasis, PSA nadir). We assessed correlations with Spearman rank, and differences between groups with Mann-Whitney U test, setting significance levels at p=0.05. Analyses were performed using SPSS (22.0;IBM).

Results

Table 8.1 presents baseline characteristics. Thirty-three patients had a solitary metastasis on PET/CT (n=25 lymph node, n=8 bone); 4 had two (nodal) metastases, and 3 presented with three metastases, (n=1 all lymph nodes, n=1 all bone, n=1 lymph node and bone). Median follow-up and PFS after SBRT were 32.6 (IQR 14.7-50.3) and 11.5 (95%CI 8.4-14.6) months, respectively. Compared to patients without a post-SBRT PSA nadir, patients with a PSA nadir had a HR for progression of 0.23 (p<0.001).

Median (IQR) $MATV_{highest,}$ $MATV_{total,}$ $SUV_{mean\text{-}pvc}$, $TLCU_{highest\text{-}pvc}$, and $TLCU_{total\text{-}pvc}$ were 2.3 (1.5-3.7), 2.6 (1.6-4.3), 4.3 (3.2-5.8), 9.5 (5.5-17.5), and 10.5 (5.9-22.7), respectively. The lesion-based MATV and $TLCU_{pvc}$ were significantly higher for bone compared to lymph nodes (Table 8.2). The presence of >1 metastasis on [^{18}F]-fluoromethylcholine PET/CT had a HR of 2.74 (p=0.03) for progression. All PET semi-quantitative parameters were significantly correlated (p≤0.013). There was no PET parameter threshold on ROC analysis (supplemental data). No semi-quantitative PET/CT parameter predicted PFS, but a trend in risk of progression for large MATV was noted (HR=1.86; p=0.10) (Table 8.3).

We assessed potential associations of PET quantitative parameters with clinical data (supplemental data). Several SUV and TLCU variants were significantly higher for patients with PSA levels above median (3.75 ng/ml) at PET/CT (p=0.01-0.04). For Gleason score and pre-treatment with ADT we found no significant association with quantitative PET parameters.

Table 8.1: Patient characteristics.

Characteristic	
Age at metastases	
Mean±SD	67±6.7 years
Time from diagnosis to metastases	
Median (IQR)	46.2 (12.0-81.8) months
Gleason score	
5	2 (5%)
6	5 (13%)
7	16 (41%)
8	10 (26%)
9	6 (16%)
TNM-stage at diagnosis	
Stage 2	20 (51%)
Stage 3	16 (41%)
Stage 4	3 (8%)
Primary treatment	
Surgery	25 (63%)
Surgery + radiotherapy	4 (10%)
Radiotherapy	5 (13%)
Radiotherapy + hormone therapy	3 (8%)
Brachytherapy	3 (8%)
Lymph node dissection	
Yes	13 (33%)
No	27 (68%)
PSA at metastases	
Median (IQR)	3.75 (2.43-6.80) ng/ml
Type of metastases	
Bone	9 (23%)
Lymph node	30 (75%)
Bone + Lymph node	1 (3%)

Table 8.2: Lesion-based values of PET parameters. Data are presented as median with IQR.

	All lesions (n=50)	Lymph node (n=37)	Bone (n=13)	p-value[a]
MATV	2.21 (1.58-3.28)	1.92 (1.40-2.74)	3.46 (2.68-8.96)	<0.001
$SUV_{mean\text{-}pvc}$	3.93 (3.01-5.34)	3.72 (3.12-5.25)	4.45 (2.80-5.55)	0.816
$TLCU_{pvc}$	8.39 (5.24-15.43)	7.43 (4.77-13.06)	12.68 (7.52-50.33)	0.009

[a]Lymph node vs. bone

Table 8.3: Results from survival analyses. Significant differences in bold.

		PFS (95%CI)	HR (95%CI)	p-value[b]
PET parameters:				
$MATV_{highest}$	< 2.3 mL	14.3 (2.8-25.8)	1.86 (0.87-3.97)	0.103
	≥ 2.3 mL	9.5 (8.5-10.5)		
$MATV_{total}$	< 2.6 mL	12.1 (4.4-19.9)	1.66 (0.78-3.51)	0.181
	≥ 2.6 mL	9.5 (6.8-12.3)		
$SUV_{mean\text{-}pvc}$	< 4.3	11.5 (6.8-16.2)	0.99 (0.47-2.00)	0.969
	≥ 4.3	9.5 (5.8-13.3)		
$TLCU_{highest\text{-}pvc}$	< 9.5	9.4 (1.3-17.4)	0.98 (0.48-1.99)	0.944
	≥ 9.5	11.5 (8.6-14.4)		
$TLCU_{total\text{-}pvc}$	< 10.5	9.4 (1.2-17.6)	0.98 (0.48-2.00)	0.955
	≥ 10.5	11.5 (8.6-14.4)		
number of metastases	=1	11.5 (8.1-15.0)	2.74 (1.06-7.11)	**0.031**
	>1	6.5 (2.6-10.4)		
lesion type[a]	lymph node	11.5 (7.2-15.8)	1.37 (0.61-3.09)	0.436
	bone	9.5 (6.3-12.7)		
Gleason score	≤ 7	13.4 (9.6-17.2)	1.81 (0.86-3.81)	0.112
	> 7	8.5 (3.9-13.2)		
PSA at PET/CT	< 3.75 ng/ml	9.4 (4.7-14.1)	0.86 (0.42-1.74)	0.670
	≥ 3.75 ng/ml	11.5 (8.7-14.4)		
PSA nadir after SBRT	no	3.5 (2.6-4.5)	0.23 (0.11-0.50)	**<0.001**
	yes	12.1 (9.8-14.5)		
pre-SBRT ADT	no	11.5 (8.7-14.3)	0.85 (0.29-2.43)	0.753
	yes	6.5 (0.0-15.0)		

[a]lesion with highest uptake in case of >1 lesion; [b]from log rank-test.

Discussion

The number of metastases at [^{18}F]-fluoromethylcholine PET/CT predicted progression after SBRT for recurrent hormone-sensitive oligometastatic prostate cancer, but other (quantitative) PET measures did not.

In patients receiving ADT for treatment of hormone-sensitive prostate cancer recurrence a similar association between number of metastases and survival has been reported, and at biochemical recurrence after primary therapy the disease burden (number of [^{18}F]-fluoromethylcholine PET/CT positive lesions) was an independent prognostic factor for developing castration-resistant disease (*14-16*).

[^{18}F]/[^{11}C]-labelled choline PET/CT is one of the preferred methods for restaging at biochemical progression (*1,17*), with a prevalence of oligometastatic disease of 40-91% (*14,18-21*). However, other PET tracers (e.g. PSMA-ligands) may detect more metastases, especially at low PSA values (*22,23*). Schwenck et al. observed that in 27% of patients with oligometastases on choline PET/CT, PSMA

detected more lesions, resulting in their re-classification as non-oligometastatic (*23*). In our study, 11/40 patients (27.5%) had no initial PSA response after SBRT (presence of PSA nadir: HR 0.23; p<0.001), which may reflect suboptimal metastasis detection rates for [^{18}F]- fluoromethylcholine PET/CT in this setting. However, whether PSMA-guided management will improve patient outcomes remains to be shown.

Limitations of this study are its retrospective nature and relatively small sample size. A strength is its clinical relevance - and PET/CT imaging, SBRT, and PSA follow-up (tested at least every 3 months) were all performed according to institutional protocols used in clinical practice.

The role of post-SBRT ADT or the relative benefits of SBRT to only PET positive lesion(s) versus larger volume irradiation (e.g. the involved lymph node chain) remains to be investigated. Further research is also warranted to characterize the time-course of activity in treated lesions on post-SBRT [^{18}F]-fluoromethylcholine PET/CT scans, and to avoid over-diagnosing local failure (Figure 8.1).

In conclusion, the number of detected oligometastases seems prognostic. Additional data, including from prospective randomised controlled trials (e.g. NTC01558427 and NTC02680587), will hopefully determine whether the advantage of SBRT for oligometastatic prostate cancer is limited to deferring systemic therapy and identify additional patient or tumour characteristics predictive for disease progression.

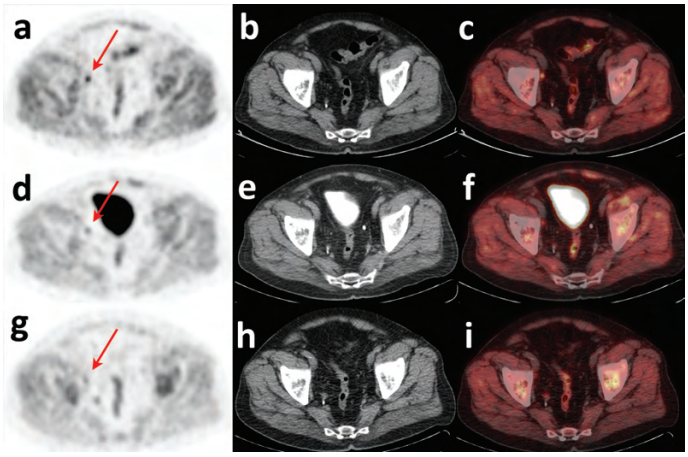

Figure 8.1: [^{18}F]-fluoromethylcholine PET/CT images of a 74-year-old patient with persisting, but decreasing, activity in a right para-iliac lymph node after SBRT. PET, low-dose CT, and fused PET/CT images before (A-C) SBRT, 20 months (D-F) and 32 months (G-I) after SBRT, respectively.

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Supplemental files

Supplemental Table 8.1: Patient-based values of PET parameters. Data is presented as median with IQR.

SUV_{mean}	2.9 (2.2-3.7)
SUV_{max}	4.9 (3.4-6.7)
SUV_{peak}	3.1 (2.2-4.7)
$TLCU_{highest}$	6.6 (3.6-12.1)
$TLCU_{total}$	7.1 (4.0-14.8)

Supplemental Table 8.2: Lesion-based values of PET parameters. Data is presented as median with IQR.

	All lesions (n=50)	**Lymph node (n=37)**	**Bone (n=13)**	**p-value***
SUV_{mean}	2.75 (2.10-3.50)	2.55 (2.10-3.31)	3.39 (2.11-4.28)	0.237
SUV_{max}	4.59 (3.07-5.88)	4.50 (3.02-5.61)	5.16 (3.30-7.04)	0.347
SUV_{peak}	2.79 (2.12-4.05)	2.63 (1.99-3.51)	3.89 (2.25-5.43)	0.099
TLCU	5.64 (3.51-10.90)	5.07 (3.29-9.33)	10.09 (5.54-41.79)	**0.004**

*Lymph node vs. bone

Supplemental Table 8.3: Results from ROC analysis at median PFS (11.5 months).

	11.5 month PFS		
	AUC	p	cut-off
$SUV_{mean-pvc}$	0.41	0.34	4.2
SUV_{mean}	0.41	0.34	7.4
SUV_{max}	0.42	0.40	4.6
SUV_{peak}	0.44	0.50	1.7
$MATV_{highest}$	0.51	0.92	1.8
$MATV_{total}$	0.56	0.50	1.8
$TLCU_{highest-pvc}$	0.44	0.51	4.6
$TLCU_{total-pvc}$	0.47	0.77	4.6
$TLCU_{highest}$	0.45	0.57	3.0
$TLCU_{total}$	0.49	0.87	3.0

Supplemental Table 8.4: Results from survival analyses.

		PFS (95%CI)	**HR (95%CI)**	**p-value#**
SUV_{mean}	< 2.9	9.4 (2.1-16.6)	0.87 (0.43-1.76)	0.694
	≥ 2.9	11.5 (7.9-15.2)		
SUV_{max}	< 4.9	9.4 (2.1-16.6)	0.88 (0.43-1.79)	0.722
	≥ 4.9	11.5(7.9-15.2)		
SUV_{peak}	< 3.1	9.4 (2.1-16.6)	0.89 (0.44-1.81)	0.751
	≥ 3.1	11.5 (7.9-15.2)		
$TLCU_{highest}$	< 6.6	9.4 (1.2-17.6)	1.00 (0.49-2.03)	0.990
	≥ 6.6	11.5 (8.6-14.4)		
$TLCU_{total}$	< 7.1	9.4 (1.2-17.6)	1.00 (0.49-2.03)	0.990
	≥ 7.1	11.5 (8.6-14.4)		

#from log-rank

Supplemental Table 8.5: Patient-based subgroup analysis of PET parameters. Data is presented as median with IQR. Significance level was set at p<0.05. Significant differences in bold.

	Gleason score		No. of metastases		ADT pre-SBRT		PSA at FCH-PET/CT	
	≤ 7	> 7	1	> 1	No	Yes	< 3.75	≥ 3.75
$MATV_{highest}$	2.71 (2.70)	2.14 (1.65)	2.16 (2.02)	3.46 (4.99)	2.17 (1.97)	4.94 (8.95)	2.02 (1.41)	3.12 (5.16)
p-value	0.420		0.218		0.118		0.072	
$MATV_{total}$	2.71 (3.92)	2.46 (2.31)	2.16 (2.02)	7.42 (6.46)	2.20 (2.46)	8.06 (12.59)	2.27 (1.50)	4.22 (7.67)
p-value	0.899		**0.002**		0.071		0.174	
SUV_{mean}	3.13 (2.06)	2.58 (1.21)	2.78 (1.79)	3.10 (1.43)	2.85 (1.43)	3.32 (3.46)	2.45 (1.10)	3.44 (2.41)
p-value	0.177		0.507		0.592		**0.023**	
$SUV_{mean-pvc}$	4.45 (2.31)	3.61 (2.24)	4.30 (2.84)	4.24 (2.14)	4.25 (2.55)	4.35 (3.75)	3.70 (1.72)	4.70 (2.59)
p-value	0.159		0.651		0.956		0.056	
SUV_{max}	5.16 (3.41)	3.87 (2.64)	4.97 (3.39)	4.86 (2.84)	4.79 (3.33)	5.53 (4.54)	4.32 (2.15)	5.98 (4.65)
p-value	0.114		0.754		0.868		**0.040**	
SUV_{peak}	3.10 (2.86)	2.83 (1.78)	3.05 (2.44)	3.37 (2.55)	3.06 (2.30)	4.45 (4.38)	2.52 (1.31)	4.45 (3.89)
p-value	0.263		0.363		0.517		**0.030**	
$TLCU_{highest}$	9.00 (18.51)	4.87 (6.49)	5.72 (9.07)	9.85 (37.56)	5.80 (7.44)	25.10 (48.93)	4.63 (4.92)	10.25 (36.41)
p-value	0.168		0.277		0.184		**0.015**	
$TLCU_{highest-pvc}$	12.39 (23.58)	7.99 (7.84)	9.20 (12.37)	12.68 (44.95)	9.31 (10.76)	29.85 (59.93)	7.19 (6.64)	15.09 (44.07)
p-value	0.128		0.277		0.255		**0.014**	
$TLCU_{total}$	9.00 (18.51)	6.72 (10.09)	5.72 (9.07)	18.19 (44.74)	6.72 (9.81)	26.99 (57.69)	5.41 (5.42)	11.16 (36.95)
p-value	0.420		**0.022**		0.159		**0.035**	
$TLCU_{total-pvc}$	12.39 (25.31)	9.38 (13.63)	9.20 (12.37)	24.09 (54.44)	9.53 (12.22)	32.41 (71.45)	8.87 (7.21)	16.57 (45.04)
p-value	0.329		**0.016**		0.184		**0.033**	